IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

DEY, L.P. and DEY, INC.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	
	)	C.A. No. _____
SEPRACOR INC.,	)	
	)	
Defendant,	)	

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs, Dey, L.P. and Dey, Inc. (collectively "Dey") for its complaint for a declaratory judgment against Defendant, Sepracor Inc. ("Sepracor"), allege as follows:

INTRODUCTION

1. This is a declaratory judgment action seeking a declaration of non-infringement of United States Patent No. 6,451,289 ("the '289 patent"). Defendant Sepracor filed the '289 patent along with United States Patent Nos. 5,362,755, 5,547,994, 5,760,090, 5,844,002, and 6,083,993 (collectively "the method-of-use patents"), with the Food and Drug Administration ("FDA") for listing in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), as patents that could reasonably be asserted against anyone marketing or seeking to market a generic levalbuterol hydrochloride inhalation solution. In July 2005, Dey filed an Abbreviated New Drug Application ("ANDA") with the FDA seeking approval to market 3 mL generic levalbuterol hydrochloride inhalation solution products ("3mL levalbuterol"). Under the applicable statutory scheme, Dey cannot get final approval for its 3mL levalbuterol until entry of an order of non-infringement or invalidity on all of the patents asserted against the company filing the first ANDA for 3mL levalbuterol.

2. Breath Limited ("Breath") was the first to file an ANDA on 3mL levalbuterol. Sepracor sued Breath for infringement of all six of the Orange Book listed patents. Sepracor and Breath settled their litigation without the entry of an order signed by the Court finding each of the six patents invalid or not infringed. Until 180 days after Breath chooses to market its 3mL levalbuterol, or 75 days after the entry of a final order finding each of the six patents invalid or not infringed, the FDA is prohibited from granting final approval to any ANDA for 3mL levalbuterol. Under its settlement agreement with Sepracor, Breath's license to market a 3mL levalbuterol will not take effect until August 20, 2012, unless another generic company enters the market earlier. A copy of Sepracor's press release regarding the settlement is attached as Exhibit 1.

3. Sepracor sued Dey on the five method-of-use patents. It did not sue Dey on the '289 patent. Because the '289 patent is listed in the Orange Book and the Breath case has settled without a finding that the '289 patent is invalid or not infringed, the FDA is prohibited from granting final approval to Dey's tentatively approved 3mL levalbuterol. Accordingly, Dey seeks entry of a declaratory judgment that the manufacture, use, or sale of its ANDA product does not infringe any valid claim of the '289 patent.

THE PARTIES

4. Plaintiff Dey, L.P. is a Delaware limited partnership having a principal place of business at 2751 Napa Valley Corporate Drive, Napa, California. Dey, L.P.'s registered agent for service of process in Delaware is the Corporation Trust Company, 1209 Orange Street, Wilmington, Delaware, 19801.

5. Plaintiff Dey, Inc. is a Delaware corporation having a principle place of business at 2751 Napa Valley Corporate Drive, Napa, California. Dey, Inc's registered agent for service

of process in Delaware is the Corporation Trust Company, 1209 Orange Street, Wilmington, Delaware, 19801.

6. On information and belief, Defendant Sepracor, Inc. is a company organized and existing under the laws of the State of Delaware, with its principal place of business at 84 Waterford Drive, Marlborough, Massachusetts, 01752.

JURISDICTION AND VENUE

7. This action is brought under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.,* and 21 U.S.C. § 355(j)(5)(B), based upon an actual controversy between the parties to declare that Dey is free to continue to seek final FDA approval of ANDA No. 77-800, and upon approval by the FDA, to manufacture, use, market, sell, offer to sell, and/or import its proposed levalbuterol hydrochloride solution products as described in the ANDA.

8. This Court has original jurisdiction over the subject matter of this Action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

9. This Court has personal jurisdiction over Sepracor because Sepracor is a Delaware corporation with a registered office in Delaware and/or because Sepracor has designated an agent in Delaware for service of process.

10. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and 1400(b) and by Sepracor's choice of forum in related case C.A. No. 06-113-JJF.

PATENT IN SUIT

11. On its face the '289 patent entitled "Albuterol Formulations" indicates it was issued by the United States Patent and Trademark Office on November 8, 1994 and is owned by Sepracor. The '289 patent claims, *inter alia,* a levalbuterol hydrochloride solution product that is free of chelating agents. A copy of the '289 patent is attached to this complaint as Exhibit 2.

THE APPLICABLE LAW

12. In December 2003, Congress passed the Medicare Modernization Act of 2003 ("MMA"). Title XI of that Act entitled "Access to Affordable Pharmaceuticals," made certain changes to the Hatch Waxman Act. The changes included a provision allowing an ANDA applicant to bring a declaratory judgment action for invalidity or non-infringement of an Orange Book listed patent if the NDA holder does not sue within 45 days of receiving notice of a Paragraph IV Certification. 21 U.S.C. § 355(j)(5)(B).

13. The MMA also added forfeiture provisions for the 180-day exclusivity awarded to the first to file pursuant to the Hatch Waxman Act. 21 U.S.C. § 355(j)(5)(D). The forfeiture provisions require, *inter alia*, the entry of a judgment of non-infringement or invalidity with respect to all of the patents asserted against the first to file whether or not those patents are asserted against subsequent ANDA filers. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb).

ACTS GIVING RISE TO THE ACTION

14. Upon information and belief, Sepracor is the current holder of approved New Drug Application ("NDA") No. 20-837 for XOPENEX® (levalbuterol hydrochloride) inhalation solution.

15. According to the Orange Book listings, XOPENEX®, or treatment methods using XOPENEX®, are claimed in the method-of-use patents and the '289 patent.

16. In a letter dated January 9, 2006, and addressed to Sepracor, Dey gave written notice that it had submitted to the FDA, ANDA No. 77-800 which contained "Paragraph IV Certifications," pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV). In particular, pursuant to ANDA No. 77-800 and Dey's Paragraph IV Certifications, Dey notified Sepracor that Dey intends to engage in the commercial manufacture, use and sale of the proposed 3mL levalbuterol that is the subject of ANDA No. 77-800.

17. On or about February 22, 2006, Sepracor filed in the District of Delaware an action against Dey for patent infringement of five of the six Orange Book listed patents (the method-of-use patents) under 35 U.S.C. §§ 271(e)(2) and 281. Sepracor alleged that the act of infringement relates to, *inter alia*, Dey's filing of ANDA 77-800 for approval to market 3mL levalbuterol.

18. Sepracor further alleged that upon FDA approval of Dey's ANDA No. 77-800, Dey will infringe one or more claims of the method-of-use patents by making, offering to sell, selling and/or importing Dey's 3mL levalbuterol in the United States, and/or by actively inducing and/or contributing to the infringement by others.

19. Sepracor did not allege that Dey's filing of ANDA 77-800 for approval to market 3mL levalbuterol would infringe the '289 patent or that upon FDA approval of ANDA No. 77-800, Dey will infringe one or more claims of the '289 patent by making, offering to sell, selling and/or importing Dey's 3mL levalbuterol in the United States, and/or by actively inducing and/or contributing to the infringement of others.

20. Breath was the first company to file an ANDA on 3mL levalbuterol. On October 21, 2005, Sepracor filed suit against Breath in the District of Massachusetts (the "Massachusetts case"). In its complaint, Sepracor alleged, *inter alia*, that manufacture, use or sale of the Breath ANDA product would infringe all six of the Orange Book listed patents—the five method-of-use patents and the '289 patent.

21. On May 1, 2008 the Massachusetts case settled without the entry of a judgment or order executed by a court finding that the six patents in suit were invalid or not infringed. The order of dismissal signed by the Judge in the Massachusetts case contains no finding of invalidity or non-infringement of the method-of-use patents or the '289 patent.

22. Until the entry of a judgment or an order of no infringement or invalidity is signed and entered by a court with respect to all six of the patents Breath was sued on—including the '289 patent – which Dey was not sued on—Breath's exclusivity will not be triggered and Dey's ANDA product, which does not infringe any valid claim of the six Orange Book patents, will be kept off the market, depriving the general public the availability of a low-cost generic 3mL levalbuterol product.

23. A declaration of rights between the parties is necessary to establish that Dey has not, does not and will not infringe any valid and/or enforceable claim of the '289 patent.

COUNT I

DECLARATORY JUDGMENT OF NON-INFRINGEMENT OF THE '289 PATENT

24. Dey repeats each of the foregoing paragraphs as if fully set fourth herein.

25. There is a substantial and continuing controversy between Sepracor and Dey and a declaration of rights is both necessary and appropriate to establish that Dey does not infringe any claim of the '289 patent.

26. The '289 patent claims, *inter alia*, a levalbuterol hydrochloride solution that does not contain chelating agents. *See* Exhibit 2.

27. There are four independent claims in the '289 patent—claims 1, 2, 11 and 12. Each of these claims requires that there be no chelating agent in the claimed formulation. Claim 1 discloses a formulation "free of chelating agents." *See* '289 patent, col. 5 ll. 49-50. Claims 2, 11 and 12 disclose a formulation that "does not contain a chelating agent." *See* col. 6 ll. 4-5, ll. 44-45 and ll. 56-57.

28. The levalbuterol hydrochloride solution that is the subject of Dey's ANDA No. 77-800 contains EDTA. *See* ANDA, section 3.2.P.2.1.2 attached hereto as Exhibit 3. EDTA is a

chelating agent. *See id.* The product that is the subject of Dey's ANDA No. 77-800 cannot, therefore, infringe any claim of the '289 patent.

29. Because the product that is the subject of ANDA 77-800 contains a chelating agent, the manufacture, marketing, use, offer for sale, sale and/or importation of the product that is the subject of Dey's ANDA 77-800 will not directly infringe, induce or contribute to the infringement by others of the '289 patent, nor can the claims of the '289 patent be infringed by the filing of Dey's ANDA 77-800.

COUNT II

DECLARATORY JUDGMENT OF INVALIDITY OF THE '289 PATENT

30. Dey repeats each of the foregoing paragraphs as if fully set forth herein.

31. There is a substantial and continuing controversy between Sepracor and Dey as to the validity of the '289 patent.

32. The '289 patent is invalid under 35 U.S.C. §§ 101 *et seq.* including §§ 101, 102, 103 and/or 112.

PRAYER FOR RELIEF

WHEREFORE, Dey respectfully requests that the Court enter judgment as follows:

A. Declaring that the claims of the '289 patent have not been infringed by the filing of Dey's ANDA 77-800;

B. Declaring that the manufacture marketing, use, offer for sale, sale and/or importation of the product that is the subject of Dey's ANDA 77-800 will not directly infringe, or induce or contribute to the infringement by others of any claims of the '289 patent;

C. Declaring that the '289 patent is invalid;

D. Awarding Dey attorneys' fees and costs; and

E. Awarding Dey such other and further relief as the Court may deem just and proper.

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Dated: June 20, 2008

EXHIBIT 1

Press Release

Sepracor Announces Final Settlement of XOPENEX(R) Inhalation Solution Patent Infringement Litigation with Breath Limited

MARLBOROUGH, Mass.--(BUSINESS WIRE)--May 1, 2008--Sepracor Inc. (Nasdaq: SEPR) today announced that it has entered into a Settlement and License Agreement with Breath Limited (Breath), an Arrow Group subsidiary, to resolve the patent litigation involving Sepracor's XOPENEX(R) brand levalbuterol HCl Inhalation Solution products (1.25 mg/3 mL, 0.63 mg/3 mL and 0.31 mg/3 mL). The agreement permits Breath to launch generic versions of these XOPENEX Inhalation Solution dosages under terms of an exclusive license commencing on August 20, 2012. Upon launch, Breath would pay Sepracor a double-digit royalty on gross profits generated from the sales of generic versions of these XOPENEX Inhalation Solution dosages. The parties will promptly file a dismissal without prejudice in the United States District Court for the District of Massachusetts that will conclude this litigation.

Sepracor and Breath also contemporaneously entered into a Supply Agreement whereby, effective August 20, 2012, Sepracor will exclusively supply levalbuterol HCl products (1.25 mg/3 mL, 0.63 mg/3 mL and 0.31 mg/3 mL) to Breath, under Sepracor's New Drug Application (NDA), for a period of 180 days and on a non-exclusive basis for a period of time thereafter. In addition to the royalties described above, Breath will pay Sepracor on a cost plus margin basis for supply of the levalbuterol HCl products. Both the exclusive license under the Settlement and License Agreement and the exclusive supply obligations under the Supply Agreement could become effective prior to August 20, 2012 if a third party launches a generic version of those dosages of XOPENEX Inhalation Solution or if the parties otherwise mutually agree.

"We are very pleased to have reached a resolution of our dispute with Breath, which allows both parties to avoid the uncertainties and significant expenses related to complex patent litigation," said Adrian Adams, President and Chief Executive Officer of Sepracor Inc. "With this lawsuit behind us, Sepracor can continue to focus on leveraging the many opportunities that lay ahead with respect to our current product portfolio and our growing research and development pipeline, in addition to our efforts directed toward achieving success with the recently launched OMNARIS(TM) Nasal Spray product and the expected launch of ALVESCO(R) Inhalation Aerosol later this year."

"We are very pleased to be able to settle this matter," said Ian McAffer, Managing Director of Breath Limited. "This settlement will provide us with the certainty of being in a position to introduce versions of the XOPENEX Inhalation Solution products on a date certain without the burden of litigation."

The settlement agreement is a final settlement of the Breath litigation. The settlement with Breath does not end all disputes related to generic XOPENEX Inhalation Solution products, as litigation against Dey L.P. and Barr Laboratories, Inc. remains pending. In compliance with U.S. law, the Settlement and License Agreement and Supply Agreement will be submitted to the U.S. Federal Trade Commission and Department of Justice and are subject to their review.

About Sepracor

Sepracor Inc. is a research-based pharmaceutical company dedicated to treating and preventing human disease by discovering, developing and commercializing innovative pharmaceutical products that are directed toward serving unmet medical needs. Sepracor's drug development program has yielded a portfolio of pharmaceutical products and candidates with a focus on respiratory and central nervous system disorders. Currently marketed products include LUNESTA(R) brand eszopiclone, XOPENEX(R) brand levalbuterol HCl Inhalation Solution, XOPENEX HFA(R) brand levalbuterol tartrate Inhalation Aerosol, BROVANA(R) brand arformoterol tartrate Inhalation Solution and OMNARIS (TM) brand ciclesonide Nasal Spray. Sepracor's corporate headquarters are located in Marlborough, Massachusetts.

Forward-Looking Statement

This news release contains forward-looking statements that involve risks and uncertainties, including statements with respect to the timing of introduction of generic versions of XOPENEX Inhalation Solution; Sepracor leveraging opportunities with respect to its current product portfolio and its growing research and development pipeline; achieving success with OMNARIS Nasal Spray; and the expected launch of ALVESCO Inhalation Aerosol later this year. Among the factors that could cause actual results to differ materially from those indicated by such forward-looking statements are: Sepracor's ability to fund, and the results of, further clinical trials with respect to products under development; the timing and success of submission, acceptance, and approval of regulatory filings; the scope of Sepracor's trademarks, patents and the patents of others and the success of challenges by others of Sepracor's patents; the clinical benefits and commercial success of the company's products; Sepracor's ability to realize the

benefits of its sales force realignment and to expand its sales force capacity to accommodate the launches of OMNARIS Nasal Spray and ALVESCO Inhalation Aerosol; the ability of the company to attract and retain qualified personnel; the ability of the company to successfully collaborate with third parties; the performance of Sepracor's licensees and other collaboration partners; and certain other factors that may affect future operating results that are detailed in Sepracor's annual report on Form 10-K for the year ended December 31, 2007 filed with the Securities and Exchange Commission.

In addition, the statements in this press release represent Sepracor's expectations and beliefs as of the date of this press release. Sepracor anticipates that subsequent events and developments may cause these expectations and beliefs to change. However, while Sepracor may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Sepracor's expectations or beliefs as of any date subsequent to the date of this press release.

For a copy of this release or any recent release, visit Sepracor's web site at www.sepracor.com.

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"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995: Statements in this press release regarding Sepracor Inc.'s business which are not historical facts are "forward-looking statements" that involve risks and uncertainties. For a discussion of such risks and uncertainties, which could cause actual results to differ from those contained in the forward-looking statements, see "Risk Factors" in the Company's Annual Report or Form 10-K for the most recently ended fiscal year.

EXHIBIT 2

US006451289B2

(12) **United States Patent**
Wherry, III et al.

(10) **Patent No.: US 6,451,289 B2**
(45) **Date of Patent: Sep. 17, 2002**

(54) **ALBUTEROL FORMULATIONS**

(75) Inventors: **Robert J. Wherry, III**, Nashua, NH (US); **Stewart H. Mueller**, Sudbury, MA (US)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/815,150**

(22) Filed: **Mar. 22, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/191,910, filed on Mar. 24, 2000.

(51) **Int. Cl.**[7] **A61K 9/12**; A61K 31/135

(52) **U.S. Cl.** **424/45**; 424/401; 514/653; 560/42; 206/204

(58) **Field of Search** 424/45, 401; 560/42; 206/204; 514/653

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,206,758 A		6/1980	Hallworth et al.	128/203
4,353,365 A		10/1982	Hallworth et al.	128/203
4,499,108 A		2/1985	Sequeira et al.	514/653
4,751,071 A		6/1988	Magruder et al.	424/467
4,777,049 A		10/1988	Magruder et al.	424/457
4,851,229 A		7/1989	Magruder et al.	424/457
5,362,755 A		11/1994	Barberich et al.	514/649
5,545,745 A	*	8/1996	Gao et al.	560/42
6,113,927 A	*	9/2000	Hatakeyama	424/401
6,119,853 A	*	9/2000	Garrill et al.	206/204

OTHER PUBLICATIONS

Schering, Drug Information on Proventil®, revised Aug. 1999 (obtained through on–line PDR).*

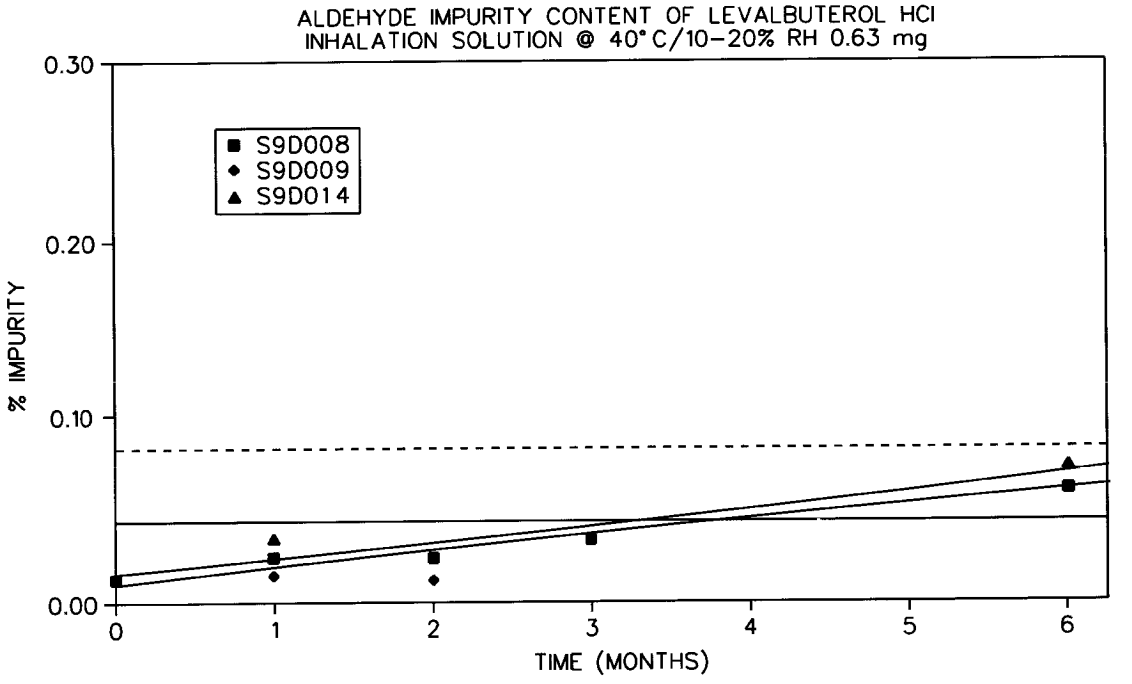
* cited by examiner

Primary Examiner—Jose' G. Dees
Assistant Examiner—M. Haghighatian
(74) *Attorney, Agent, or Firm*—Heslin Rothenberg Farley & Mesiti P.C.; Mary Louise Gioeni

(57) **ABSTRACT**

Albuterol formulations packaged in an oxygen-permeable plastic container have a long shelf life at room temperature. The formulations consist essentially of albuterol or a pharmaceutically acceptable salt thereof, sodium chloride, and water, have a pH of about 4, and contain less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen.

20 Claims, 3 Drawing Sheets



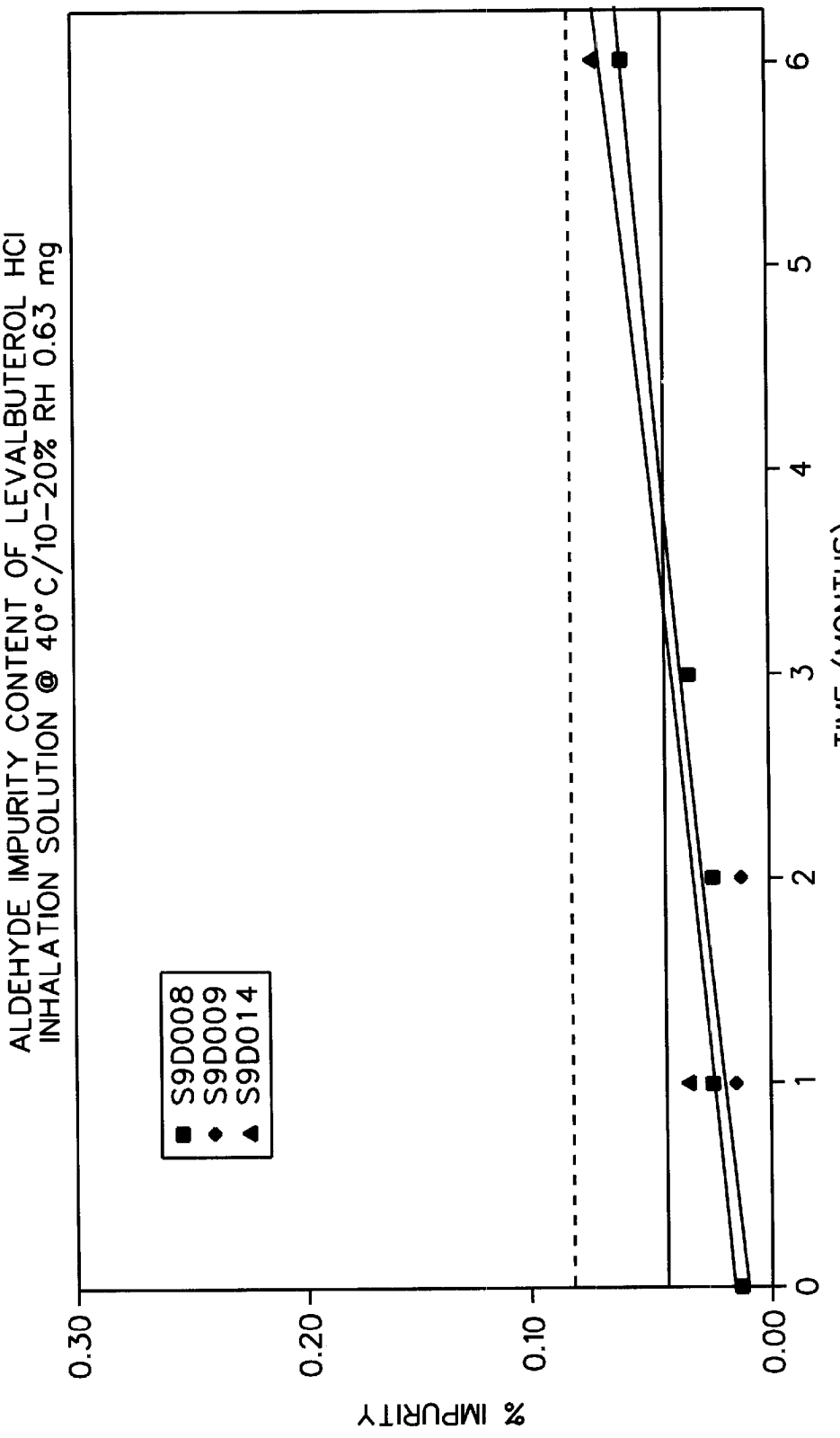

ALDEHYDE IMPURITY CONTENT OF LEVALBUTEROL HCl
INHALATION SOLUTION @ 40°C/10–20% RH 0.63 mg
S9D008
S9D009
S9D014
% IMPURITY
0.30
0.20
0.10
0.00
0
1
2
3
4
5
6
TIME (MONTHS)

fig. 1

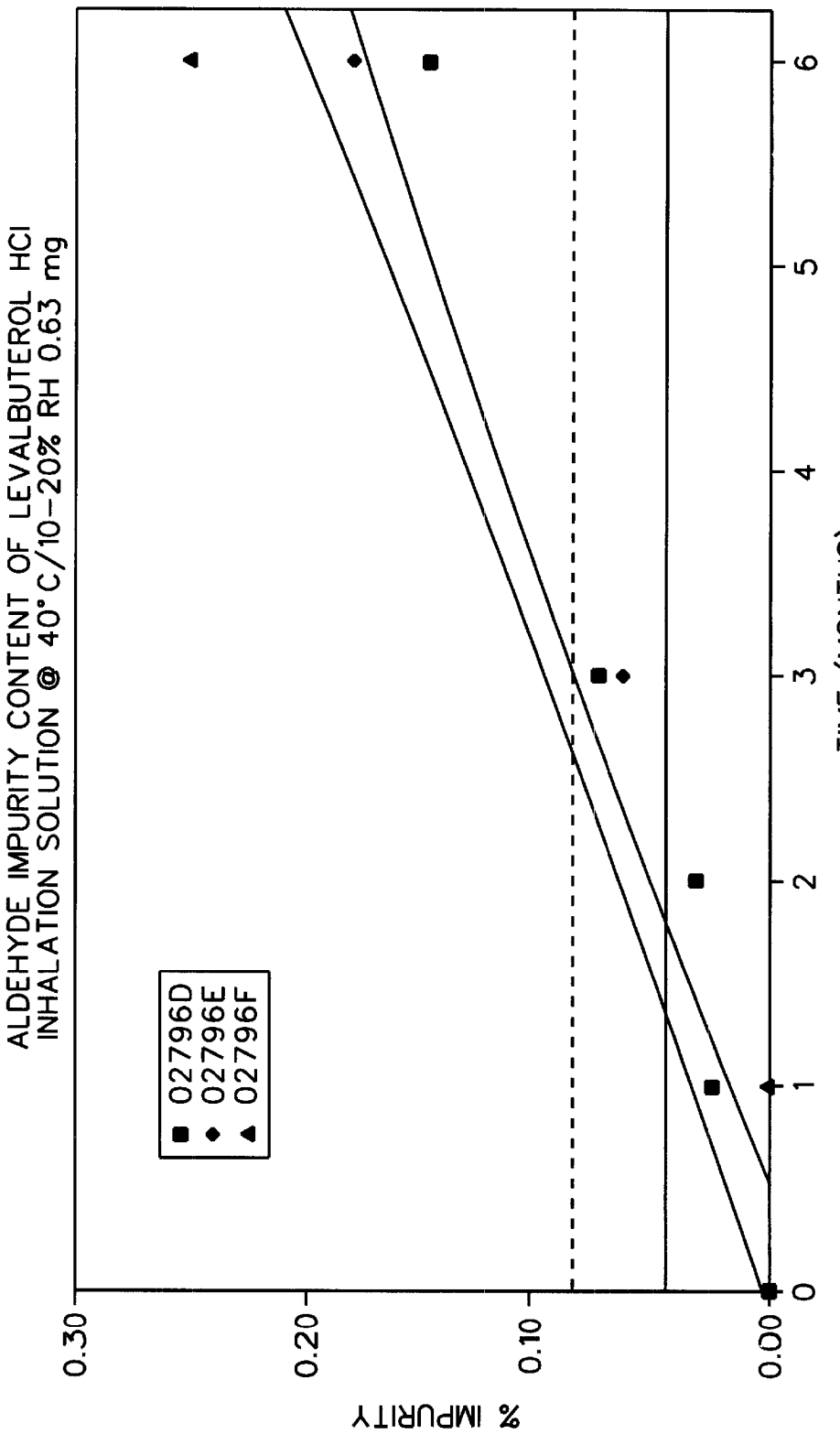

ALDEHYDE IMPURITY CONTENT OF LEVALBUTEROL HCl
INHALATION SOLUTION @ 40°C/10–20% RH 0.63 mg
02796D
02796E
02796F
% IMPURITY
0.30
0.20
0.10
0.00
0
1
2
3
4
5
6
TIME (MONTHS)

fig. 2

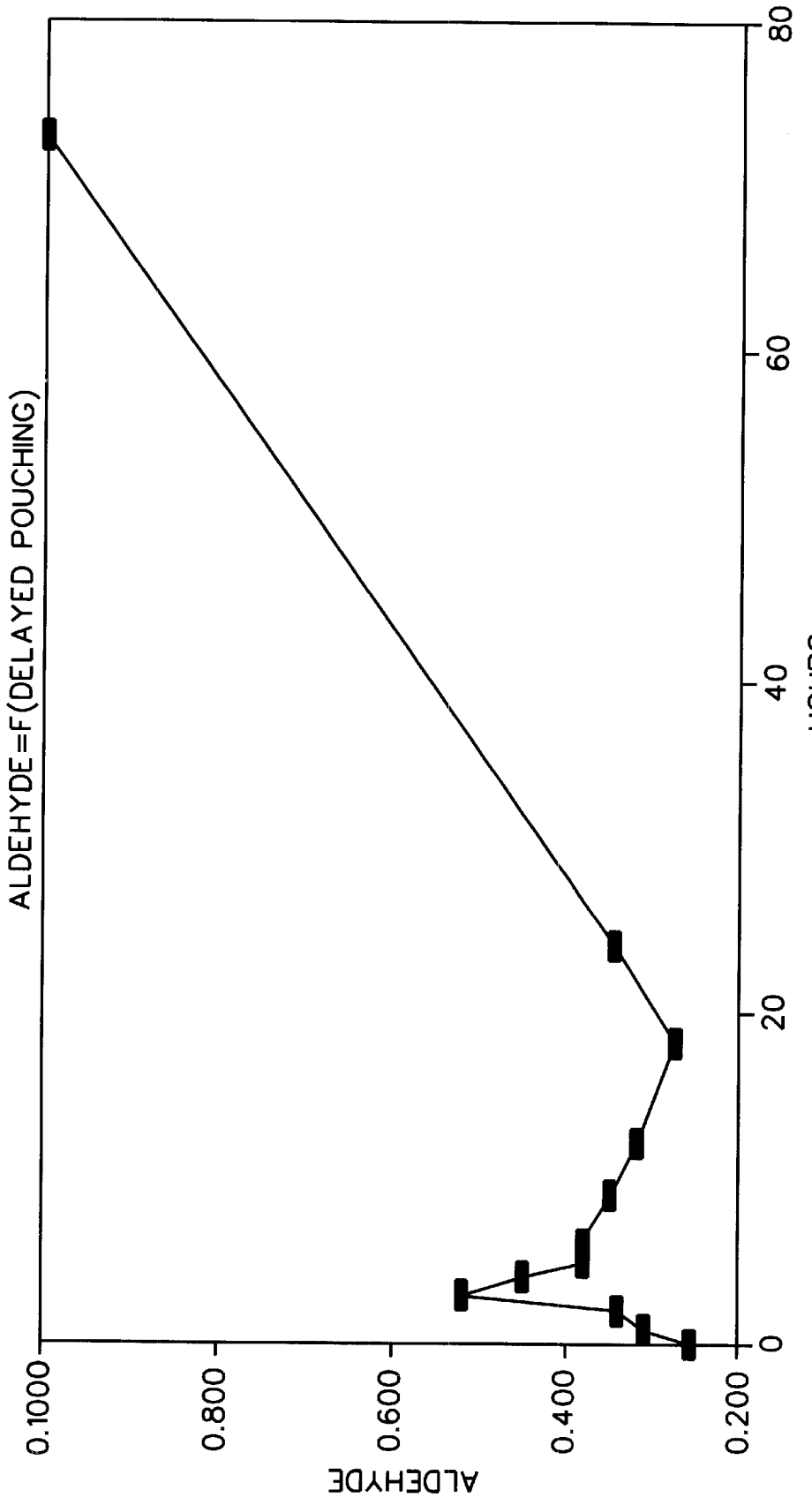

ALDEHYDE=F(DELAYED POUCHING)
ALDEHYDE
0.1000
0.800
0.600
0.400
0.200
0
20
40
60
80
HOURS

fig. 3

ALBUTEROL FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/191,910, filed Mar. 24, 2000.

FIELD OF THE INVENTION

The invention relates to packaged albuterol formulations having a long shelf life.

BACKGROUND OF THE INVENTION

An attractive method for aseptic packaging of sterile pharmaceutical solutions is an automated process called blow-fill-seal (BFS) technology, wherein plastic containers are formed, filled and sealed in one continuous operation with limited need for human intervention. An advantage of this technology is that the opportunity for microbial contamination is minimized. It has been used for the production of unit dosage vials containing albuterol.

Albuterol is an optically active compound which can exist as an (R)- or an (S)-enantiomer, or as a mixture of the two enantiomers. The term albuterol commonly refers to a racemic mixture of (R)- and (S)-albuterol. Herein, the term albuterol is defined as including a racemic mixture, a single enantiomer of albuterol, or any mixture of enantiomers of albuterol. Albuterol is a β-adrenergic antagonist and acts to relax smooth muscle. It is, therefore, particularly effective as a bronchodilator in the treatment of asthma. Racemic albuterol and racemic albuterol sulfate are commercially available as Proventil®, Ventolin® and Vormax®. The pure (R)-enantiomer, which has the generic name levalbuterol, is commercially available as Xopenex®.

It is known that albuterol degrades in aqueous solution. (See, for example, U.S. Pat. No. 4,499,108, which relates to albuterol sulfate syrups that are stable upon prolonged storage.) The cause(s) and mechanisms of the degradation reaction(s) are not well understood, but it is known that albuterol aldehyde is one of the degradation products. The level of albuterol aldehyde in an albuterol formulation for inhalation is regulated by the Food and Drug Administration because of the potentially negative effects of administering an aldehyde compound to a patient by inhalation. Currently, a maximum of 0.05% by weight albuterol aldehyde is allowed in an albuterol formulation at the time of release, with a maximum of 0.08% at the end of the expiration date. Therefore, formation of albuterol aldehyde in an aqueous albuterol solution limits the shelf life of the package containing it.

One drawback of using BFS technology for formulations of albuterol is that it has been difficult to produce a packaged formulation having a long shelf life without including additives such as chelating agents, sequestering agents, antioxidants or preservatives in the formulation or storing the package at temperatures below room temperature. It is therefore an object of the invention to provide a method of maximizing the shelf life of an albuterol formulation packaged using BFS technology.

SUMMARY OF THE INVENTION

It has been surprisingly found that when nitrogen is used as the blowing or ballooning gas in a BFS process for packaging an albuterol formulation, a package having a long shelf life is obtained. In this respect, the present invention relates to a method for manufacturing a packaged albuterol formulation having a long shelf life comprising:

blowing nitrogen gas through a hollow cylinder of an oxygen-permeable plastic and molding the hollow cylinder into an oxygen-permeable container, thereby at least partially enclosing a reduced oxygen atmosphere;

filling the oxygen-permeable container with an aqueous formulation of albuterol, or a pharmaceutically acceptable salt thereof, the aqueous formulation containing less than 0.05% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen;

enclosing the oxygen-permeable container in a reduced oxygen atmosphere within an oxygen-impermeable wrapper to produce a package enclosing an atmosphere containing less than about 2% oxygen; whereby the amount of albuterol aldehyde contained in the aqueous formulation remains lower than 0.08% by weight for a period of at least 12 months at room temperature.

In another aspect, the present invention relates to stable packaged pharmaceutical formulations consisting essentially of:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

water;

the formulation having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, enclosed within an oxygen-permeable plastic container, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months. Preferably, the oxygen-permeable plastic container additionally encloses a gas phase comprising less than about 5% oxygen. The oxygen-permeable plastic container is preferably enclosed within a sealed wrapper comprising an oxygen-impermeable material. More preferably, the sealed wrapper additionally encloses a gas phase contained within the sealed wrapper and comprising less than about 5% oxygen.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot of % albuterol aldehyde vs. time for an albuterol formulation packaged using nitrogen as the ballooning gas.

FIG. **2** is a plot of % albuterol aldehyde vs. time for an albuterol formulation packaged without using nitrogen.

FIG. **3** is a plot of % albuterol aldehyde vs. delay time for an albuterol formulation wherein containers were filled with the formulation and wrapping of the containers was delayed. % Albuterol aldehyde was determined after storage at 40° C. for three months.

DETAILED DESCRIPTION OF THE INVENTION

According to the method of the present invention, an aqueous solution of albuterol that has a low level of dissolved oxygen is prepared for packaging. No chelating agent, sequestering agent, antioxidant, or preservative, such as edetate disodium, sodium citrate, or benzalkonium chloride, is included in the formulation. The albuterol utilized in the solution may be racemic albuterol, a single enantiomer of albuterol, or a mixture of enantiomers of albuterol. It may be in the form of the free amine or a pharmaceutically acceptable salt thereof. In a preferred embodiment, (R)-albuterol is used. (R)-Albuterol is defined as containing at least 95% by weight (R)-albuterol, preferably greater than 98% (R)-albuterol, and more preferably greater than 99% (R)-albuterol.

In another preferred embodiment, the (R)-albuterol is in the form of a pharmaceutically acceptable salt. Pharmaceu-

tically acceptable salts of albuterol include, for example, acid addition salts such acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, and p-toluenesulfonic. The hydrochloride salt is especially preferred for (R)-albuterol; the sulfate is preferred for racemic albuterol.

An exemplary formulation, suitable for administration to an adult by inhalation is:

1.4 mg (R)-albuterol hydrochloride

27 mg sodium chloride

3 mL water

A lower dosage may be provided by reducing the amount of (R)-albuterol hydrochloride to 0.7 mg, while keeping the amounts of sodium chloride and water the same. Typical pediatric formulations contain 0.18 mg to 0.36 mg (R)-albuterol hydrochloride per 3 mL unit dose. Oxygen is displaced from the bulk solution by sparging with nitrogen until an oxygen level of less than 1 ppm, preferably, 500 ppb, and more preferably, 300 ppb, is attained. A nitrogen blanket is maintained over the bulk solution until the solution is packaged.

A package for the formulation is made up of an oxygen-permeable container and an oxygen-impermeable wrapper that encloses one or more of the containers. For example, a preferred container is a unit dose vial composed of low density polyethylene (LDPE). In a preferred embodiment, a plurality of unit dose vials are enclosed within an oxygen-impermeable wrapper composed of a foil laminate.

The containers are typically fabricated, filled and sealed using BFS technology. (For an overview of BFS technology, see Oschman, R. and Schubert, O. E., *Blow-Fill-Seal Technology,* CRC Press, 1999.) A plurality of unit dose vials (UDV) is typically formed, filled and sealed simultaneously. An extrudable, oxygen-permeable plastic or resin, preferably LDPE, is used to form the containers. First, the resin is extruded into an opened blow mold in the form of parallel hollow cylinders. The mold plates are closed and simultaneously seal the bottom. A blowing or ballooning gas is passed through the cylinders to maintain the opening in the cylinders while a vacuum is applied through tiny holes in the walls of the mold to fill the mold and form the containers. In prior art processes, compressed air has been used to form the containers, in contrast to the method of the present invention. Nitrogen is used as the ballooning gas in order to reduce the oxygen level in the headspace of the containers being formed. The albuterol solution is measured into the containers and sealed. Typically, the oxygen level is reduced to about 14% in the headspace or gas phase enclosed within the containers.

The vials are then enclosed in a protective oxygen-impermeable wrapper. A material that is impermeable to oxygen and that can be sealed to exclude oxygen may be used. Barrier materials that can prevent the transmission of oxygen are well known in the art and include commercially available polymer films and metallic foils such as aluminum foil. Laminates composed of one or more barrier materials and one or more films of a non-barrier polymer may also be used. A suitable material, for example, is a laminated foil composed of layers of polyester, aluminum foil and polyethylene. As the pouch is sealed, nitrogen is blown into the interior of the pouch, reducing the level of oxygen in the interior of the sealed pouch to less than about 2%.

After the pouch is sealed, oxygen diffuses from the headspace of the vials into the interior of the pouch until an equilibrium is reached at less than about 5% oxygen in the headspace of both the vials and the pouch. The diffusion occurs over a period of time and may take as long as two weeks.

It has been unexpectedly found that packages manufactured without using nitrogen as the ballooning gas have higher levels of albuterol aldehyde over time than those produced using nitrogen. In addition, when nitrogen was used as the ballooning gas, but wrapping of the vials was delayed, higher levels of albuterol aldehyde can result.

EXAMPLES

Example 1

A solution of (R)-albuterol was prepared according to the formula:

1.44 mg (R)-albuterol hydrochloride

27 mg sodium chloride

3 mL water.

The pH of the solution was adjusted with sulfuric acid. The solution was sparged with nitrogen until the level of oxygen was less than 500 ppb. The tank was blanketed with nitrogen.

The solution was packaged in unit dose vials using a BFS method. A set of twelve vials were formed simultaneously from LDPE using nitrogen as the ballooning gas and then filled with the solution. A pouch composed of a laminate of aluminum foil, polyester and polyethylene was formed around the set of filled UDVs. A wand for the delivery of nitrogen was placed inside the assembly, and nitrogen was blown into the pouch as it was being formed and sealed. The level of oxygen in the airspace in the pouch was reduced to less than 2%. Pouches thus manufactured were held at 40° C. and samples were withdrawn at intervals of 1, 2, 3, and 6 months and tested for levels of albuterol aldehyde. Results are displayed graphically in FIG. **1**. The graph shows that the level of albuterol aldehyde was below the FDA release limit of 0.05% initially and remained below 0.08% for at least six months. This corresponds to a shelf life of at least 12 months at room temperature.

Example 2

A solution of (R)-albuterol was prepared as in Example 1. The solution of (R)-albuterol was then packaged in unit dose vials as in Example 1, except that nitrogen was not used as the ballooning gas. The UDVs were wrapped in a laminated foil pouch with nitrogen, also as in Example 1.

Pouches were held at 40° C. and samples were withdrawn at intervals of 1, 2, 3, and 6 months and tested for levels of albuterol aldehyde. Results are displayed graphically in FIG. **2**. The graph shows that the level of albuterol aldehyde rose above 0.08% in less than three months. This corresponds to a shelf life of significantly less than 12 months at room temperature.

Example 3

A solution of (R)-albuterol was prepared and packaged as in Example 1, except that pouching of the UDVs was delayed. Levels of albuterol aldehyde in the solution were measured for various delay times. Results are tabulated below and displayed graphically in FIG. **3**. The results indicate that delayed pouching can increase the level of albuterol aldehyde in the solution.

TABLE 1

Delayed Pouching of UDVs: % Albuterol Aldehyde After 3 Months 40 C/15% RH

Sample Type:	Replicate #:	Albuterol Aldehyde Values
Positive Control	1	0.03
	2	0.02
	3	NA
Negative Control	1	0.10
	2	0.09
	3	0.11
1 Hour	1	0.03
	2	0.03
	3	0.03
2 Hour	1	0.03
	2	0.04
	3	0.03
3 Hour	1	0.06
	2	0.03
	3	0.06
4 Hour	1	0.05
	2	0.05
	3	0.03
5 Hour	1	0.05
	2	0.03
	3	0.03
6 Hour	1	0.04
	2	0.04
	3	0.03
9 Hour	1	0.04
	2	0.03
	3	0.03
12 Hour	1	0.03
	2	0.03
	3	0.03
18 Hour	1	0.02
	2	0.03
	3	0.03
24 Hour	1	0.03
	2	0.03
	3	0.04

What is claimed is:

1. A method of manufacturing a packaged albuterol formulation having a shelf life of at least twelve months; said method comprising:

blowing nitrogen gas through a hollow cylinder of an oxygen-permeable plastic and molding the hollow cylinder into an oxygen-permeable container, thereby at least partially enclosing a reduced oxygen atmosphere;

filling the oxygen-permeable container with an aqueous formulation of albuterol, or a pharmaceutically acceptable salt thereof, said aqueous formulation being free of chelating agents, sequestering agents, antioxidants, and preservatives, and containing less than 0.05% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen;

enclosing the oxygen-permeable container under an atmosphere containing less than about 2% by weight oxygen within an oxygen-impermeable wrapper to produce a package enclosing an atmosphere containing less than about 2% by weight oxygen, and which does not contain an oxygen-absorbent.

2. A stable packaged preservative-free pharmaceutical formulation consisting essentially of:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

water;

said formulation having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, enclosed within an oxygen-permeable plastic container, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.

3. A stable packaged pharmaceutical formulation according to claim **2** wherein said oxygen-permeable plastic container additionally encloses a gases phase comprising less than about 5% oxygen.

4. A stable packaged pharmaceutical formulation according to claim **2** wherein said oxygen-permeable plastic container is enclosed within a sealed wrapper comprising an oxygen-impermeable material.

5. A stable packaged pharmaceutical formulation according to claim **4** wherein said sealed wrapper additionally encloses a gas phase contained within the sealed wrapper and comprising less than about 5% by weight oxygen.

6. A stable packaged pharmaceutical formulation according to claim **4** wherein a plurality of oxygen-permeable plastic containers are enclosed within said sealed wrapper.

7. A stable packaged pharmaceutical formulation according to claim **2** wherein said albuterol is (R)-albuterol.

8. A stable packaged pharmaceutical formulation according to claim **7** wherein said pharmaceutically acceptable salt is (R)-albuterol hydrochloride.

9. A stable packaged pharmaceutical formulation according to claim **2** wherein said oxygen-impermeable material is a foil laminate.

10. A stable packaged pharmaceutical formulation according to claim **2** wherein said oxygen-permeable material is low density polyethylene.

11. A preservative-free unit dosage formulation for administration by inhalation consisting essentially of:

0.18–1.4 mg albuterol or a pharmaceutically acceptable salt thereof;

27 mg sodium chloride; and

2–4 mL water;

said unit dosage formulation having a pH of about 4, containing less than 1 ppm dissolved oxygen and containing less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said unit dosage formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.

12. A stable, preservative-free packaged pharmaceutical formulation, packaged according to the method of claim **1**, said formulation comprising:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said formulation does not contain a ch elating agent, a sequestering agent, an antioxidant, or a preservative. agent, an antioxidant, or a preservative.

13. A stable, preservative-free packaged pharmaceutical formulation according to claim **12**, wherein said albuterol is (R)-albuterol.

14. A stable, preservative-free packaged pharmaceutical formulation according to claim **12** wherein said pharmaceutically acceptable salts is (R)-albuterol hydrochloride.

15. A stable, preservative-free packaged pharmaceutical formulation according to claim **12** wherein said oxygen-impermeable material is a foil laminate.

16. A stable, preservative-free packaged pharmaceutical formulation according to claim **12** wherein said oxygen-permeable material is low density polyethylene.

17. A method according to claim **1** wherein said albutrol is (R)-albuterol.

18. A method according to claim **1** wherein said pharmaceutically acceptable salt is (R)-albuterol hydrochloride.

19. A method according to claim **1** wherein said oxygen-impermeable wrapper comprises a foil laminate.

20. A method according to claim **1** wherein said oxygen-permeable container comprises low density polethylene.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,451,289 B2
DATED : September 17, 2002
INVENTOR(S) : Wherry, III et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6,
Line 1, delete the word "permeable"
Line 58, delete "agent, an antioxident, or a preservative."

Signed and Sealed this

Twelfth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT 3

FILED UNDER SEAL

JS 44 (Rev. 3/99)

CIVIL COVER SHEET

The JS-44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS

DEY, L.P. and DEY, INC.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

DEFENDANTS

SEPRACOR INC.

County of Residence of First Listed _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

(c) Attorney's (Firm Name, Address, and Telephone Number)

John G. Day
Ashby & Geddes
500 Delaware Avenue, 8th Floor
Wilmington, DE 19801 (302) 654-1888

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

		DEF			DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury—Med. Malpractice
- ☐ 365 Personal Injury—Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence
- Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

V. ORIGIN (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION (Cite the U.S. Civil Statute under which you are filing and write brief statement of cause. Do not cite jurisdictional statutes unless diversity.)

The Declaratory Judgments Act (28 U.S. Code §§ 2201 and 2202) and the patent laws of the United States (Title 35, U.S. Code).

VII. REQUESTED IN COMPLAINT: ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 DEMAND $ declaratory relief CHECK YES only if demanded in complaint: JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY (See instructions): JUDGE Joseph J. Farnan, Jr. DOCKET NUMBER 06-113 (consolidated)

DATE June 20, 2008 SIGNATURE OF ATTORNEY OF RECORD

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 08-372

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 1 COPIES OF AO FORM 85.

6/20/08
(Date forms issued)

(Signature of Party or their Representative)

JOHN D RITTER
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action